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EXAMINER	
CROUCH, DEBORAH	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/082,804	MCCONLOGUE ET AL.	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-34 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-34 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 22 February 2002 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 8/20/02.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 1-34 are pending.

The specification states "Games, supra" in the specification. However, there is no "Games" full citation in the specification (see page 11, parag. 59 as an example). Applicant is advised that amending the specification for the full citation may raise issues under new matter. A response to this objection should provide supporting evidence in the specification for such an amendment.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-34 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

Claims 1-34 lack either a specific or substantial utility. The nonhuman animal is disclosed as being normal in a variety of observances (see specification, pages 13-14). The animal is disclosed as being useful to test and evaluate the toxicity, structure activity relationships and usefulness of compounds that might be potential BACE1 inhibitors (specification, page 17, parag. 77) or for screening for an inhibitor of the production by a protease other than β-secretase of a peptide recognized by an antibody that recognizes amino acid residues 13-28 of Aβ (specification, page 5, parag. 27, lines 1-3). Further, the specification discloses methods for using the animal as an assay system for the disclosed testing and screening. These utilities are not seen as either specific or substantial. For the discussion below, applicant should refer to MPEP 2107.01.

Specific Utility

> A "specific utility" is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. Office personnel should distinguish between situations where an applicant has disclosed a specific use for or application of the invention and situations where the applicant merely indicates that the invention may prove useful without identifying with specificity why it is considered useful. For example, indicating that a compound may be useful in treating unspecified disorders, or that the compound has "useful biological" properties, would not be sufficient to define a specific utility for the compound. Similarly, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. A general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed. Contrast the situation where an applicant discloses a specific biological activity and reasonably correlates that activity to a disease condition. Assertions falling within the latter category are sufficient to identify a specific utility for the invention. Assertions that fall in the former category are insufficient to define a specific utility for the invention, especially if the assertion takes the form of a general statement that makes it clear that a "useful" invention may arise from what has been disclosed by the applicant. Knapp v. Anderson, 477 F.2d 588, 177 USPQ 688 (CCPA 1973).

The claimed animals, methods of assay using the animal lack a specific utility because the identification of other effects that a β-secretase inhibitor would have on an animal is not directed any particular effect. Like the gene probe discussed above, there is no specific target of the assay. Similarly, using the animal to screen for proteases other than β-secretases that cause the production of a protein that is recognized by an antibody, which recognizes certain residues in A/β, the Alzheimer's disease related peptide is not specifically directed at a specific protein.

Substantial Utility

> A "substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":
>
> (A) Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved;
> (B) A method of treating an unspecified disease or condition;
> (C) A method of assaying for or identifying a material that itself has no specific and/or substantial utility;

(D) A method of making a material that itself has no specific, substantial, and credible utility; and
(E) A claim to an intermediate product for use in making a final product that has no specific, substantial and credible utility.

The mice and methods of assay using the mice lack a substantial utility. The use of the mice to assay for identification of other effects that a β-secretase inhibitor would have on the mouse lacks substantial utility as there is no real-world use for the so identified proteases. The specification does not describe how one would use the identified inhibitors, or how this information could be used. The mice and methods for screening for an inhibitor of the production by a protease other than β-secretase of a peptide recognized by an antibody that recognizes amino acid residues 13-28 of Aβ also lack a substantial utility. There is no real-world use disclosed for the results of the assay. The specification does not state for what purpose the peptide would be used. In both instances, identifying an inhibitor and screening for a peptide would require further experimentation on the identified inhibitor and peptide.

The claimed cortical cell cultures, ES cells and blastocysts lack utility as the animal and the methods of identifying and screening lack a specific or substantial utility.

Claims 1-34 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 1-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The mice are described in the specification as being useful for identifying other

Two methods for producing BACE1 null mice are disclosed in the specification; one method using nuclear transfer technology and the other method using ES cell technology.

Neither of these methods was enabled at the time of filing for the bread of nonhuman animal as discussed immediately below.

At the time of filing the, art taught that it was unpredictable to clone successfully for the breath of the claims which encompasses all mammals, reptiles, fish, birds and amphibians. Even for mammals, the art taught that their cloning was unpredictable. In regard to this, Westhusin, states that one of the major factors influencing a successful cloning outcome is species of target animal. Westhusin goes on to state that while the basic methodology for nuclear transfer may be similar, the specific materials and methods do not automatically apply across all species. Westhusin outlines six factors which contribute to successful cloning: 1) acquisition of mature ova, 2) removing the chromosomes contained within the ova, 3) transfer of cell nuclei obtained from the animal to be cloned into enucleated ova, 4) activation of the newly formed embryo, 5) embryo culture in vitro, and 6) transfer of the cloned embryo into a surrogate mother. There is no guidance in the specification or the art on, for example, activation of enucleated Drosophila eggs or lobster eggs, much less how to enucleate them for successful nuclear transfer. Westhusin further states that each of these steps will vary slightly between species, but that, more importantly, the efficiency of each step varies among species, ultimately affecting the ease of which a particular animal can be cloned (Westhusin, page 36-37, bridg. parag.). This analysis is supported by Polejaeva that states, in regard to the inefficiency of cloning, that several factors affect the inefficiency: laboratory to laboratory variation, oocyte source and quality, methods of embryo culture, donor cell type, possible loss of somatic imprinting in the nuclei of the reconstructed embryo, failure to reprogram the transplanted nucleus adequately, and failure of artificial methods of activation to emulate reproducibly those crucial membrane-mediated events that accompany fertilization (Polejaeva, page 1, parag. 2). Thus nuclear transfer, at the time of filing was not routine, but requires extensive

experimentation without a predictable degree of success. Pennisi and several scientists working in the area of mammalian cloning point to a lack of general and reproducible success emphasize this. Robert Wall of the USDA is quoted as stating that despite years of effort, "[w]e're in the same bind that we've always been in. A majority of [would be clones] do not make it to term." (Pennisi, page 1722, col. 1, parag. 2, lines 9-14). Pennisi and Vogel state, "even when an embryo does successfully implant in the womb, pregnancies often end in miscarriages" (Pennisi, page 1722, col. 1, parag. 3, lines 16-18). Attempts to clone pigs using techniques successful in sheep were not successful; indicating that cross-species application of methodology is unpredictable (Pennisi, page 1725, col. 1-2, bridg. parag.). The case with rabbits indicates that obtaining an embryo by nuclear transfer does not translate into a cloned rabbit. While many cloned rabbit embryos can be made, they abort upon transfer to surrogate mothers, and in 2000, there had not been any successes in cloning rabbits (Pennisi, page 1725, col. 2, parag. 3). With primates, two cloned monkeys were produced, but there have been no subsequent successes in primate cloning (Pennisi, page 1726, col. 2, line 6 to col. 3, line 3). With regard to cats, one cloned cat has been produced, but given the difficulty in the art to produce a cloned cat and the lack of producibility as stated above, the cloning of cats is unpredictable. Two attempts to implant cat eggs or reconstructed embryos failed, providing for an unpredictable outcome for cat cloning (Pennisi, page 1726, col. 2, parag. 3, lines 4-5). Others have reported establishing pregnancies but no report of a cloned cat being born (Pennisi, page 1726, col. 2, parag. 3, lines 5-9 and 11-12). As the authors state, establishing pregnancies is only part of the problem and is not a guarantee of a cloned mammal being produced (Pennisi, page 1726, col. 2, lines 9-11). In additional support of the lack of predictability for the cloning of nonhuman primates, is a report that the cloning of monkeys, a primate, by nuclear transfer had been successful when embryonic cells were the nuclear donor, not when somatic cells

were used as nuclear donor (Mitalipov, abstract). Mitalipov further states, clearly, that somatic cell cloning, as is part of the present methods, has not been accomplished in primates (Mitalipov, page 1367, col. 2, parag, 3, lines 1-3). Simerly, states that in rhesus monkey NT units, DNA and microtubule imaging showed disarrayed mitotic spindles with misaligned chromosomes, which resulted in unequal chromosome segregation and aneuploid embryos (Simerly, page 297, col. 2, parag. 1, lines 5-11).

It was known at the time of filing, that cross-species nuclear transfer was unpredictable in both embryo and term development. Meirelles demonstrate that methods of nuclear transfer where the nuclear material of *Bos indicus* is inserted into the oocyte of *Bos taurus* produces calves comprising the nuclear material of *Bos indicus* and the mitochondria of *Bos taurus*. Meirelles *et al*. teach that previous attempts to use the *Bos* oocyte as hosts for nuclear transfer from unrelated species allowed development to the blastocyst stage, however conclude that incompatibility among the nuclear and mitochondrial genetic systems is responsible for the early arrest. Meirelles *et al*. also point to similar failures using *Mus caroli* and *Mus musculus* citing Dominko *et al*. discussed in length in the previous office action. Meirelles *et al*. conclude that in light of their results and the failures of the prior art, that nuclear transfer across subspecies barriers is possible. (see Meirelles, pp. 351-355). The present specification encompasses nuclear transfer (cloning) when the nucleus is of one species and the oocyte is of another species. This clearly lacks predictability given the teachings of Meirelles. Further, in the production of sheep goat chimeras, there were biases towards chimeras whose genotype and phenotype was most like that of the recipient, and that the successful production of chimeras resided in the neutralization of incompatibility between the chimeric embryo (Fehilly et al (1985), page 221, parag. 1). This is also an unpredictable feature of the claimed invention as an embryo of one species implanted into a surrogate mother of another species is unlikely to develop

given the teaching of Fehilly. The specification does not provide guidance on producing cross-species embryo or animals, nor how to overcome the unpredictable nature of cross-species cloning.

With regards to choice of cell for disruption of a gene of interest, the art taught at the time of filing that the cell would need to undergo significant divisions in the selection process. Clark teaches that only primary somatic cells have been used to successfully in gene targeting experiments to produce livestock having a disrupted gene of choice (Clark, page 265, col.2, parag. 1, lines 12-15.) In addition, Clark teaches that about 45-population doubling are required to generate targeted cells (Clark, page 268, col. 2, parag. 1, lines 1-5). Dennig teaches, unlike ES cells, primary cells have limited proliferation capacity and any genetic modifications and nuclear transfer must be accomplished prior to senescence (Denning, page 222, col. 1, lines 5-8). To complicate matters, successful nuclear transfer in livestock has only been accomplished using primary somatic cells (Denning, page 224, col. 1, parag. 2, lines 1-4). Further, a comparison of separate Black Welsh sheep primary cell fibroblast cultures showed vast differences in the number of doublings prior to senescence; 110 doublings versus 40 doublings (Denning, page 224, col. 2, lines 16-19). In a similar analysis of pig primary cultures of fibroblasts, as in the sheep study pig fibroblasts, unlike their sheep counter part, underwent a crisis after 40 population doublings and had an unstable karyotype (Denning, page 224, col. 2, parag. 4 line 4 to page 225, col. 1, line 8). Additional studies of cell cultures prepare from fetal pig organs (gut, kidney, lung and mesonephros showed that these cells senesced or entered crisis after even fewer doublings than the fibroblast cultures (page 225, col. 1-2, bridg. sent.). The art further taught at the time of filing, that the even if sufficient population doublings could be achieved for selection, many of the pure sheep targeted clones senesced before they could be expanded for nuclear transfer, meaning that targeting frequency was lower than expected (page 228, col.

1-2, bridg. sent.). Similar experiments in pigs demonstrated that all the clones senesced, and no targeted cells for nuclear transfer were obtained. Denning also points to their own work in producing sheep comprising a disruption of the α1,3-galactosyltransferase gene, live births were achieved but the animals died within two weeks of birth (Denning, page 230, col. 1, parag. 2, lines 1-8). However, Denning reports that McCreath achieved live birth and survival of two gene targeted sheep with disruptions in different genes (Denning, page 230, col. 1, parag. 2, lines 9-12). Based on the analysis of Denning, it is possible that for gene targeted sheep, the success depends on unknown factors, whereas in pigs, the use of fibroblasts to produce gene-targeted pigs is not possible (Denning, page 230, col.1, parag. 1, lines 7-13). Thus, at the time of filing, it was unpredictable, given the data from a comparison of sheep and pig fibroblasts, that unknown factors had a detrimental impact on the production of fibroblasts comprising null mutations in targeted genes, such that the method is rendered unpredictable without undue experimentation.

Wheeler's (2001) teaches putative pig ES cells, which produced two pig chimera but there is no disclosure that the chimera gave rise to a pig of the ES cell phenotype (pages 1351-1352). Further, Wheeler states, in reference to ES cells recently isolated and the production of swine and cattle chimera, "validation of totipotency of these embryo-derived ES cell lines awaits conformation (page 1351, parag. 1, last sentence). Prelle (1999) states many embryo-derived cell lines resemble morphologically mouse ES cells, and have the ability to differentiate in vitro, but there is no evidence of live born, fertile germ line chimeras in mammalian species other than mouse (page 222, col. 2, parag. 1, lines 10-16). Moreadith (1997) states several putative ES cells lines had been isolated from hamster, pig, sheep, cattle, rabbit, rat, mink, monkey and humans, but Moreadith also states that the technology in was limited to mice (page 214, col. 1, parag. 3, lines 5-12). Gardner (1997) teaches attempts had been made to produce ES cells from pre-implantation embryos in

many mammals, that cells resembling mouse ES cells morphologically, in marker expression, growth characteristics and differentiation in vitro and in vivo have been obtained, but the question left unanswered is if these cells can contribute to gamete formation, the key attribute of ES cells (page 235, col. 1, parag. 2, col. 2, lines 3). Also, Gardner summaries non-mouse ES cells in Table 1, and indicates that there is no evidence of germ line colonization in rat, rabbit, hamster, mink, rhesus monkey, pig, cow or sheep (Table 1, page 236). Germ line colonization is required to produce subsequent generations of mice comprising a disrupted RGS9 gene, to produce mice homozygous for the disruption, or to produce heterozygous mice from mice chimeric for the disruption. Thus, art clearly teaches that ES cells were not available at the time of filing for breath of applicant's claims.

The specification only provides the production of BACE1 null mice produced by the disruption of the BACE1 gene in mice. The specification provides no guidance describing any methods for the production of any other BACE1 null animals as claimed. Further, it should be noted that certain claims require that the BACE1 null animal be transgenic for an APP familial gene, in particular for APP-717. The specification discloses the production of this animal by breeding the BACE1 null animal to an animal comprising a DNA sequence encoding APP-717. However, at the time of filing, the specification and the art only disclose the APP-717 animal as being a mouse. Thus, the only double mutant animals that could possibly ever be produced is a mouse BACE1 null/APP-717.

Therefore, for the reasons presented above, the skilled artisan at the time of the instant invention would have been required to perform an undue amount of experimentation without a predictable degree of success to implement the invention as claimed.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5, 7, 8, 17, 18, 19, 20, 27-29 and 34 rejected under 35 U.S.C. 102(e) as being clearly anticipated by US 2002/0157122 A1 ('122).

'122 teaches heterozygous and homozygous transgenic mice comprising a disruption of the BACE1 gene(s) such that there is no expression of functional protease (page 22, parag. 0175). The disruption comprises a deletion in exon I of the BACE1 gene (page 22, parag. 0174, lines 10-16). In teaching the production of BACE1 knockout mice, '112 also teaches mouse embryonic stem cells lacking a nonfunctional allele of BACE1 and a mouse blastocyst lacking a functional BACE1 allele (page 22, parag. 0175). Additionally, '112 teaches primary cortical neurons prepared from the BACE1 knockout mice (page 23, parag. 0182, lines 1-2). As '112 teaches the production of homozygous mice by mating heterozygous BACE1 knockout mice, '112 inherently teaches a mouse ES cell homozygous for nonfunctional BACE1 alleles. Thus, '112 clearly anticipates the claimed invention.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7, 8, 12, 27-29, 32 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mansour (1989) Trends in Genetics Vol. 5, pp. 7-76 in view of Vassar et al (1999) Science 286, pp. 735-741.

Mansour teaches heterozygous and homozygous mice comprising a disruption of a exon 1 of the int-2 gene gene(s), and methods of making the mice by homologous recombination in mouse ES cells, where the int-2 gene(s) is functionally disrupted (Mansour, page 350, col.2, parag. 1, to page 352, col. 1, parag. 3; and page 350, figure 3b). The targeting cassette contains a neomycin resistance gene, which is a positive selection marker (Mansour, page 350, figure 3b). Mansour teaches that heterozygous and homozygous mice comprising a disruption of the hprt gene(s) can also be made using a vector targeting exon 8 for disruption (Mansour, page 350, figure 3a). Mansour provides motivation in stating the generation of specific mouse mutants by homologous recombination an be achieved; that the positive-negative selection method is general for targeting any gene, regardless of function; that little knowledge of the target locus is needed and should be applicable to any gene (page 348, col. 1, parag. 1, lines 1-4; page 348, col. 1, parag. 3, lines 1-3 and page 352, col. 2, parag. 3, lines 6-9). However, Mansour does not teach the genomic sequence for GAL1R.

Vassar teaches the cloning of a human transmembrane aspartic protease cDNA with GenBank Accession No. AF190725 (page 735, col. 3, parag. 3 to page 736, col. 1, lines 1-5 and page 736, figure 2, col. 1, parag. 2, lines 1-8). Vassar states that their cDNA encodes BACE (page 740, col.3, parag. 2, lines 1-3). Vassar offers motivation in stating that BACE1 deficient mice can be used to analyze APP cleavage in vivo and provide further evidence that the enzyme cloned is BACE (page 740, col. 1, parag. 2, lines 3-7).

Thus, at the time of the present invention it would have been obvious to the ordinary artisan to produce transgenic mice, mouse ES cells and mouse blastocysts

comprising a heterologous or a homozygous disruption of a BACE1 gene as taught by Mansour in view of Vassar, to study the effects of a BACE1 negative background on A/β production. The cited prior art provided to the ordinary artisan at the time of filing the requisite teaching, suggestion and motivation to reach the claimed invention.

Claims 1, 6, 8, 9, 27 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mansour (1989) Trends in Genetics Vol. 5, pp. 7-76 in view of Vassar et al (1999) Science 286, pp. 735-741 in view of Wattler et al (1999) BioTechniques 26, pp. 1150-1159.

Mansour teaches heterozygous and homozygous mice comprising a disruption of a exon 1 of the int-2 gene(s), and methods of making the mice by homologous recombination in mouse ES cells, where the int-2 gene is functionally disrupted (Mansour, page 350, col.2, parag. 1, to page 352, col. 1, parag. 3; and page 350, figure 3b). The targeting cassette contains a neomycin resistance gene, which is a positive selection marker (Mansour, page 350, figure 3b). Mansour teaches that heterozygous and homozygous mice comprising a disruption of the hprt gene(s) can also be made using a vector targeting exon 8 for disruption (Mansour, page 350, figure 3a). Mansour provides motivation in stating the generation of specific mouse mutants by homologous recombination an be achieved; that the positive-negative selection method is general for targeting any gene, regardless of function; that little knowledge of the target locus is needed and should be applicable to any gene (page 348, col. 1, parag. 1, lines 1-4; page 348, col. 1, parag. 3, lines 1-3 and page 352, col. 2, parag. 3, lines 6-9). However, Mansour does not teach the genomic sequence for GAL1R.

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BACE (page 740, col.3, parag. 2, lines 1-3). Vassar offers motivation in stating that BACE1 deficient mice can be used to analyze APP cleavage in vivo and provide further evidence that the enzyme cloned is BACE (page 740, col. 1, parag. 2, lines 3-7).

Wattler teaches method of conditional mutagenesis through the disruption of a gene of interest by the insertion of a marker gene flanked by frt recombinase sites using a λ phage knockout shuttle (KOS) (page 1158, col. 1, parag. 1, line 11 to col. 2, line 10 and figure 3). Wattler offers motivation in stating that all of the vectors generated with the λKOS system targeted ES cells, and that the system provides a very rapid and efficient method of constructing simple and complex targeting vectors (page 1157, col.2, parag. 1, lines 1-5).

Thus, at the time of the present invention it would have been obvious to the ordinary artisan to produce transgenic mice, mouse ES cells and mouse blastocysts comprising a heterologous or a homozygous disruption of a BACE1 gene as taught by Mansour in view of Vassar, to study the effects of a BACE1 negative background on A/β production, but modifying the method using the vector system of Wattler. The cited prior art provided to the ordinary artisan at the time of filing the requisite teaching, suggestion and motivation to reach the claimed invention.

Claims 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Farhangrazi et al (1997) NeuroReport 8, pp. 1127-113 in view of Mansour (1989) Trends in Genetics Vol. 5, pp. 7-76 and Vassar et al (1999) Science 286, pp. 735-741

Farhangrazi et al teaches the analysis in mouse primary cortical cells the role of ApoE4 in β-amyloid induced toxicity (page 1128, col. 1, parag. 1 and col. 2, parag. 2, lines 1-5). Mansour teaches heterozygous and homozygous mice comprising a disruption of a exon 1 of the int-2 gene(s), and methods of making the mice by homologous recombination in mouse ES cells, where the int-2 gene is functionally disrupted (Mansour, page 350, col.2,

parag. 1, to page 352, col. 1, parag. 3; and page 350, figure 3b). The targeting cassette contains a neomycin resistance gene, which is a positive selection marker (Mansour, page 350, figure 3b). Mansour teaches that heterozygous and homozygous mice comprising a disruption of the hprt gene(s) can also be made using a vector targeting exon 8 for disruption (Mansour, page 350, figure 3a). Mansour provides motivation in stating the generation of specific mouse mutants by homologous recombination an be achieved; that the positive-negative selection method is general for targeting any gene, regardless of function; that little knowledge of the target locus is needed and should be applicable to any gene (page 348, col. 1, parag. 1, lines 1-4; page 348, col. 1, parag. 3, lines 1-3 and page 352, col. 2, parag. 3, lines 6-9). However, Mansour does not teach the genomic sequence for GAL1R.

Vassar teaches the cloning of a human transmembrane aspartic protease cDNA with GenBank Accession No. AF190725 (page 735, col. 3, parag. 3 to page 736, col. 1, lines 1-5 and page 736, figure 2, col. 1, parag. 2, lines 1-8). Vassar states that their cDNA encodes BACE (page 740, col.3, parag. 2, lines 1-3). Vassar offers motivation in stating that BACE1 deficient mice can be used to analyze APP cleavage in vivo and provide further evidence that the enzyme cloned is BACE (page 740, col. 1, parag. 2, lines 3-7).

Thus, at the time of the present invention it would have been obvious to the ordinary artisan to produce cortical cells as taught by Farhangrazi from transgenic mice comprising a heterologous or a homozygous disruption of a BACE1 gene as taught by Mansour in view of Vassar, to study the effects of a BACE1 negative background on A/β processing. The cited prior art provided to the ordinary artisan at the time of filing the requisite teaching, suggestion and motivation to reach the claimed invention.

Claims 1, 13-19 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2002/0157122 A1 ('122) in view of Games et al (1995) Nature 373, pp. 523-527.

'122 teach heterozygous and homozygous transgenic mice comprising a disruption of the BACE1 gene(s) such that there is no expression of functional protease (page 22, parag. 0175). Additionally, '112 teaches primary cortical neurons prepared from the BACE1 knockout mice and their use in metabolic labeling studies (page 23, parag. 0182, lines 1-2). '112 further teaches the production of APP mutant mice/BACE1 null background by mating the BACE1 knockout mice with APP mutant mice (page 26, col. 2, lines 10-13). However, '112 does not teach mating the BACE1 knockout mice with a transgenic mouse comprising a familial APP. Games teaches the production of transgenic mice expressing a transgene encoding a human APP where amino acid residue 717 is a phenylalanine (page 523, col. 2, parag. 2, lines 1-4 and page 524, col. 1, lines 1-7). The mice develop hallmark features of Alzheimer's Disease: A/β plaques associated with distorted neuritis, BFAP-positive reactive astrocytes, Congo Red staining of amyloid plaques, and (page 525, col. 1, lines 15-22 and col. 2, lines 2-10). Motivation is provided by '112 using the BACE1 knockout/APP mutant mice to determine the effect BACE1 has on amyloid protein (page 26, col. 2, lines 3-10). Thus at the time of the instant invention, it would have been obvious to the ordinary artisan to produce BACE1 null/APP-717 mice given the teachings of '112 in view of Games to determine the effect of BACE1 on a familial Alzheimer's disease protein, APP-717; and also to prepare cortical cell cultures from the mice to determine the effect of the BACE1 null background on the formation of A/β in these cells. The robust Alzheimer's disease phenotypes of the Games mouse would provide motivation to determine the effect of BACE1 in the formation of Alzheimer's disease neuropathologies in a familial Alzheimer's disease model.

Claims 10, 11, 22-26 and 33 are free of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0408. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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